translation (3)

(12) INTERNATIONAL APPLICATION PUBLISHED ACCORDING TO THE COOPERATION TREATY IN THE FIELD OF PATENTS (PCT)

(19) World Organization for Intellectual Property
International Office

(43) International Date of Publication
17 May 2001 (17.05.2001)

[bar code]

(10) International Publication Number
WO 01/34122 A1

PCT

(51) International Patent Classification[7]: A61K 9/28

(21) International Application No.: PCT/FR00/03127

(22) International Filing Date:
9 November 2000 (09.11.2000)

(25) Language in which submitted: French

(26) Language in which published: French

(30) Priority information:
99/14104 10 November 1999 (10.11.1999) FR

(71) Applicant *(for all designated States except the US)*:
SANOFI-SYNTHELABO [FR/FR]; 174, avenue de France, F-75013 Paris (FR).

(72) Inventors; and
(75) Inventors/Applicants *(for the US only)*: **BUISSON, Bertrand** [FR/FR]; Impasse de la colline, Route du Castellet, F-04700 Oraison (FR). **FRANCAIS, Eric** [FR/FR]; 29, Chemin du Rupt Desnaux, F-54134 Voinemont (FR). **LANNE, Jean, Yves** [FR/FR]; 17, rue de la Course, F-33000 Bordeaux (FR), **PERRUT, Michel** [FR/FR]; 25, rue de Santifontaine, F-54000 Nancy (FR).

(74) Joint Representatives: **THOURET-LEMAITRE, Elisabeth;** Sanofi-Synthélabo, 174, avenue de France, F-75013 Paris (FR).

(81) Designated states *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated states *(regional)*: Patent ARIPO (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian Patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European Patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), Patent OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:
— *With International Search Report.*
— *Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.*

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[bar code]

WO 01/34112 A1

[Original English]
(54) Title: FILM COATING METHOD FOR TABLETS

[Original English]
(57) Abstract: The invention concerns a film coating method for tablets, characterised in that in [sic] consists in [sic] spraying on said tablets a film coating agent suspended in a fluid with supercritical pressure. The inventive method consists in [sic] continuously spraying in a film coating drum whereof the axis inclined relative to the horizontal enables a continuous circulation of tablets introduced upstream and at the top part of said drum, and after the film coating process, collected downstream and at the bottom part of said drum.

(57) Abstract: The invention relates to a film coating method for tablets, characterized in that it consists of spraying on said tablets a film coating agent suspended in a fluid at supercritical pressure. The inventive method consists of continuously spraying in a film coating drum whereof the axis inclined relative to the horizontal enables a continuous circulation of tablets introduced upstream and at the top part of said drum, and after the film coating process, collected downstream at the bottom part of said drum.

"Film coating method for tablets"

The present invention relates to, in general, a method for film coating tablets.

In particular, the invention relates to a method for film coating tablets by using a solvent at supercritical pressure, that is, a fluid in a supercritical state, or by using a subcritical liquid in view of obtaining tablets that are easy to store and to use, particularly for therapeutic purposes.

For many years, the protection of tablets intended for various uses and particularly for therapeutic uses in human or veterinary pharmacy has been ensured by means of a film coating. Indeed, this is a coating that is capable of preventing crumbling of these tablets while limiting their air moisture absorption, which would irreversibly alter the tablets and prevent good storage under normal domestic conditions. Some of these coatings also have an important role to play on the feed rate of the active ingredient(s) in the organism. This film coating makes use of mixtures of well-known compounds, such as derivatives of cellulose, certain acrylic or methacrylic polymers or co-polymers and polyethylene glycol, as well as mineral agents such as talc or titanium dioxide, and dyes. These film coating agents are suspended in a liquid which is either water when there is no incompatibility with the tablet components, particularly with the active ingredient(s) contained in the tablets, or in an organic solvent such as dichloromethane. This film coating operation is generally implemented in cylinders rotating at the horizontal axis within which the tablets are constantly agitated and subjected to very fine spraying of the suspension or the solution of the mixture of film coating agents in the chosen solvent.

However, the above tablet film coating methods are not free of disadvantages. Indeed, they necessitate the handling of organic solvents, particularly halogenated solvents, and cause the emission of potentially toxic organic solvent vapors, traces of which also remain inside the coated tablets.

In addition, film-coating methods by implementation of an aqueous solution or suspension necessitate a drying phase that may last longer than 10 hours in certain cases.

The search for a tablet film coating method that is capable of preventing the disadvantages of the prior methods while ensuring implementation in the systems or installations that are generally used in conventional film coating methods remains of paramount interest.

It is known that a fluid in a supercritical state, that is, in a state characterized either by a pressure and temperature that are respectively greater than the critical pressure and temperature in the case of a pure substance, or by a representative point (pressure, temperature) situated beyond the envelope of critical points represented on a diagram (pressure, temperature) in the case of a mixture, presents, for very many substances, a high solvent power that is incommensurable with that observed in this same fluid in the compressed gas state. It is the same with liquids called "subcritical," that is, in a state characterized either by a pressure greater than the critical pressure and by a temperature lower than the critical temperature in the case of a pure substance, or by a pressure greater than the critical pressures and a temperature lower than the critical temperatures of the components in the case of a mixture (Michel PERRUT, les Techniques de l'Ingénieur "Extraction par fluide supercritique," J2 770-1 to 12, 1999).

In addition, the significant and changeable variations in the solvent power of these fluids are utilized in numerous extraction (solid/fluid), fractionation (liquid/fluid), analytical or preparative chromatography and materials processing (ceramics, polymers, etc.) methods. Chemical or biochemical reactions are also carried out in such solvents.

For a dozen years, numerous works have been undertaken in view of producing the atomization of liquid or solid substances by using methods based on the properties of supercritical fluids, such as recrystallization methods by antisolvent effect or the rapid expansion of supercritical solutions, leading to the development of powders with very fine particle sizes, on the order of 0.1 to 10 micrometers, or even complex powders where the active ingredient is dispersed within an excipient or encapsulated in a protective agent. Furthermore, various spraying methods implementing a supercritical fluid have been developed, in particular to disperse paint, adhesive or coating droplets as described in patents US-5009367; US-5057342; US-5066522; US-5254260 and US-5197800 as well as in patents EP-0 388 923, EP-0 388 915, EP-0 421 796 and EP-0 506 067. Therefore, the organic solvent content of paints may be reduced significantly, on the order of 30 to 60%, further reducing the resulting volatile organic compound emissions, without the final quality of the coating, particularly its appearance, being altered.

One of the main advantages of the methods implementing fluids at supercritical pressure resides in the ease of producing the separation between the solvent (the fluid) and the extracts and solutes, as described in numerous publications and, for certain important aspects of implementation, in French Patent FR-2 592 488. The interesting properties of these fluids have been, in addition, used for a long time in solid-fluid extraction and liquid-fluid fractionation, as described in the article cited above. Furthermore, it is also interesting to note that a solvent at supercritical pressure not only has the property of dissolving certain compounds, a property used in the methods that have just been cited, but also of dissolving in a very significant manner in liquids and certain solids such as polymers. This faculty is used in certain spraying, impregnation or polymer foam development methods. Therefore, it is known that carbon dioxide maintained at supercritical pressure and at a temperature near its critical temperature may dissolve in current thermoplastic polymers at a rate of 10 to 30% by mass depending on the nature of the polymer, leading in addition to significant swelling of the polymer and a profound change in its physical properties, with a significant deterioration of its mechanical properties and a lowering of its glass transition temperature, which may reach 40°C in certain cases. It is also known that the sudden decompression of this fluid solution at supercritical pressure in a solid or a liquid may be produced in an atomizing spray nozzle and therefore lead to the development of solid particles, as has been described in particular in Patent Application WO-95/21688 and in various publications, citing for example the results of polyethylene glycol spraying (Weidner E., Steiner R., Knez Z., in "High Pressure Chemical Engineering," Elsevier 1996, ISBN 0-444-82475-8, p. 223-228).

The physical-chemical properties of carbon dioxide as well as its critical coordinates (critical pressure: 7.4 MPa and critical temperature: 31°C) make it the supercritical fluid of choice used as a preferred solvent in numerous applications, all the more so as it has no

toxicity and is available at a very low price in very large quantities. However, a co-solvent consisting of an organic solvent capable of significantly modifying the solvent power of this dioxide, especially as regards molecules presenting a certain polarity, is also sometimes added to the carbon dioxide, which is a non-polar solvent carried at supercritical pressure.

Such being the case, it has now surprisingly been found that it is possible to proceed with film coating of tablets from a suspension of a film-coating agent within a fluid at supercritical pressure that is sprayed on the tablets to be film coated.

Consequently, the invention relates to a method for film coating tablets, a method according to which a suspension of the film-coating agent in a fluid at supercritical pressure is sprayed on the tablets in question.

Therefore, the method of the invention is characterized by the use of particular properties of fluids at supercritical pressure in relation to polymers and liquids within which they are largely dissolved, which according to the invention will allow the easy production of a very homogeneous suspension of the film coating agent within the fluid, and on the use of these fluids at supercritical pressure as the spraying agent through a nozzle, or any other device allowing a very high pressure loss to be created, and to thereby ensure spraying of the suspension within which they are dissolved.

The method of the invention may be implemented by first making, by mechanical agitation, a very homogeneous suspension of a film coating agent within a fluid at supercritical pressure, generally carbon dioxide, then by spraying this suspension in a fine mist of droplets from which the fluid will immediately be evacuated when the operation is carried out under adequate temperature and pressure conditions, that is, at a temperature between ambient temperature and 60°C and a pressure between atmospheric pressure and 200 bar. When the method of the invention is implemented under pressure, it is generally carried out between 30 and 200 bar, preferably at a pressure between 100 and 200 bar and generally at a temperature between 30 and 60°C. Preferentially, the film coating operation is carried out under normal temperature and pressure conditions, that is, at ambient temperature and at atmospheric pressure.

This film coating will be distributed on the tablets even better, as the tablets will be subjected to continuous agitation, as has already been carried out according to conventional film coating techniques within drums rotating around their horizontal axes.

"Film coating agent" is understood to refer to any compound generally used for this purpose; that is, a compound that is capable, by covering the tablet, of forming a film or coating, or even a mixture of such compounds. This film coating may particularly have the effect of ensuring mechanical protection of the tablet against crumbling or crushing or may even constitute an enteric coating or a coating capable of causing, after administration of the tablet, extended release of the active ingredient contained in the tablet.

Usually, this film coating agent is chosen from among cellulose derivatives such as methylcellulose, ethyl cellulose, propylcellulose; hydroxylated cellulose derivatives such as hydroxymethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, hydroxypropylmethylcellulose; a microcrystalline cellulose; a polyacrylate such as an acrylate copolymer, an acrylic acid ester and methacrylic acid ester, a methylmethacrylic ester, a polyhydroxyethylmethacrylate; a polyvinyl alcohol; a polyethylene; a polypropylene, a polyethylene glycol; a polystyrene; a polyacrylamide; an ethylvinylacetate polyvinyl acetate copolymer; a polyvinyl acetate phthalate copolymer; a polyvinylpyrrolidone; titanium oxide; wax.

The film coating agent in question may be introduced as is in the supercritical fluid or preferably in the form of a suspension in one or more suitable solvents, generally of low molecular weight, chosen for example from among C_1-C_4 alcohols such as ethanol or isopropanol and C_3-C_6 esters such as ethyl acetate. However, ethanol constitutes a particularly preferred solvent.

In addition, the proportions of the solvent(s) and the film coating agent within the suspension will be properly chosen in such a way as to avoid as much as possible clogging effects of the device for implementing the method of the invention, particularly nozzles for atomizing the film coating agent suspension within the fluid at supercritical pressure. For this reason, the quantity of the film-coating agent in suspension in the solvent in question can vary from 5% to 30% of the weight of the total suspension, in particular from 10% to 20%.

According to a variation of this method, the suspension of the film-coating agent in the fluid at supercritical pressure may be facilitated by the addition to this fluid of one or more appropriate liquid co-solvents. This co-solvent, also with a low molecular weight, may be selected from among the solvents cited previously for the constitution of a film coating agent suspension in an appropriate solvent.

In this variation, the film-coating agent may be introduced as is in the fluid at supercritical pressure containing one or more co-solvents or, on the contrary, in the form of a suspension in one or more solvents such as described above.

Furthermore, the quantity of the film-coating agent in the fluid at supercritical pressure will not exceed 30% of the mass of the latter.

Usually, a co-solvent identical to that which is used to make the film coating agent suspension, particularly ethanol, is used in this variation.

The method of the invention thus described particularly comprises the advantage of avoiding the use of a film coating agent aqueous suspension, which eliminates contact of the tablets with water and the subsequent drying. Furthermore, one may therefore avoid using a film coating agent suspension in an organic solvent, which eliminates the handling of potentially toxic organic solvents, the significant emission of volatile organic compounds and the risk of contamination of the tablets by traces of these solvents. According to particularly favorable and preferred implementations of the method which is the subject of the invention, certain quantities of ethanol are used to modify the behavior of the fluid at supercritical pressure or for initially dispersing the film coating agent in order to make its handling easier.

However, the low risk of toxicity of ethanol is not absolutely comparable to that of most other organic solvents, and the quantities of this alcohol emitted into the atmosphere may be very limited according to certain implementations of the method.

Other characteristics and advantages of the method of the invention will appear in the course of the following description with reference to the attached drawings in which:

- Figure 1 schematically represents an installation for the film coating of tablets comprising a reactor for preparing the film coating agent suspension in a fluid at supercritical pressure and a film-coating drum, this installation being intended for an implementation of the method of the invention by discontinuous path.

- Figure 2 schematically represents an installation for the film coating of tablets intended for the implementation under pressure of the method of the invention by discontinuous path, more precisely a drum for film coating that is capable of being carried out at high pressure as well as a device for recycling the supercritical fluid.

- Figure 3 schematically represents an installation for the film coating of tablets and more precisely a film coating drum for implementing the method of the invention by continuous path.

- Figure 4 schematically represents an installation for the film coating of tablets and more precisely a film coating drum likely to be used at high pressure for implementing the method of the invention by continuous path.

Therefore, during an implementation of the method of the invention, by discontinuous path, in an installation such as represented in Fig. 1, the solvent fluid chosen (1), for example carbon dioxide, is compressed through an adjustable rate membrane volumetric pump (2). Thanks to the pump (3) of the same type, wherein the flow may be adjusted, a co-solvent (4) comprised of a liquid organic solvent, preferentially ethanol, may be added, if necessary, to this fluid solvent. The mixture thus compressed to the desired supercritical pressure is then reheated to the chosen temperature, generally a temperature that is near the critical temperature of the fluid solvent in a heat exchanger (5) comprised of a double tube, wherein the outer tubular part is swept by hot water at suitable temperature.

This mixture is then introduced in a reactor (6) equipped with an agitator (7) driven by an electrical motor (8) via a magnetic drive system (9).

The film coating agent suspension (10) under agitation is also introduced in the reactor (6) through a pump (11) of the same type as the previous pumps.

This suspension is generally comprised of an organic solvent in which various components of the film coating agent are dispersed, this solvent favorably being the same as that which is used as the co-solvent in the fluid solvent at supercritical pressure.

The rapid rotation of the agitator (7) therefore allows a homogeneous suspension of the film coating agent to be produced in the solvent mixture carried at supercritical pressure.

This suspension is then sent to the film coating drum (13) in which it is decompressed via an atomizing spray nozzle (12), the suspension supply line between the reactor (6) and the nozzle (12) being reheated by an electrical cord (14) in order to avoid precipitation of the film coating agent and clogging of this line. The sudden drop in pressure leads to the formation of very fine drops of liquid comprised of the film coating agent dissolved or dispersed in the organic solvent. These drops, when they collide with the tablets, cover the tablets with a film that is all the more homogeneous as these tablets are continuously agitated by the rotation of the film coating drum (13). This drum installed in a container (18) is comprised of a horizontal access cylinder whose walls are perforated with holes (15) in such a way as to allow an air flow (16) carried at a temperature from 50 to 60°C to pass through.

The organic solvent is rapidly driven by the fluid solvent brought to atmospheric pressure and by the flow of hot air (16) which allows the enthalpy necessary for the total vaporization of the organic solvent to be produced, the gas formed being evacuated by the line (17) connected to a vent.

The film coating agent is then formed uniformly and rapidly due to, first, the complete elimination of the organic solvent and the fluid solvent and secondly the continuous agitation of the tablets generally maintained at atmospheric or near-atmospheric pressure, and at ambient or near-ambient temperature, ensuring in this way a good distribution of this agent over the entire surface of these tablets.

According to a variation of the previous implementation by discontinuous path, an installation such as represented in Fig. 1 may be used, but modified according to Fig. 2, that is, an installation wherein the film coating drum (13) is installed in a container (18) designed to withstand pressure of at least 200 bar.

In this implementation, the preparation operation of the film coating agent suspension in the fluid solvent at supercritical pressure is carried out in the same equipment as previously, as well as the spraying of this suspension in the film coating drum containing the tablets generally maintained under pressure at a pressure between 30 and 200 bar, for example a pressure on the order of 150 bar and at a suitable temperature, generally between 30 and 60°C, for example between 45 and 55°C. However, no hot air is injected as in the discontinuous method above, but a flow of fluid solvent (1) carried at a temperature from 30 to 60°C is injected. The flow leaving the film coating drum, comprised of a mixture of fluid solvent, co-solvent and the solvent implemented to develop the film coating agent solution, is then decompressed to a pressure on the order of 45 bar, via a dump type valve (19). This decompression leads to demixing of the mixture that is admitted into a separator assembly (20) (21) comprised of, according to the system described in patent FR 2592488 cited previously, cyclonic chambers allowing the total separation of the liquid phase and the gaseous phase with provision of heat via the separator walls. For this purpose, the double-wall of these separators is traversed by the hot water, which allows the enthalpy required to ensure vaporization of the fluid solvent to be supplied. The liquid phase is then extracted at atmospheric pressure through a system of air locks (22) (23) operating according to the system described in Patent FR 2592488 already cited. The fluid solvent, thus largely free from the solvent and co-solvent utilized, may be recycled. For this purpose, it is liquefied in a double-pipe exchanger (24) whose exterior tubular part is traversed by a mixture cooled to around 0°C, such as a water/ethylene glycol mixture.

The fluid solvent is then stored at the liquid state around 5°C in a reservoir (25) whose level is maintained in a stable manner by the addition of fluid solvent from an exterior tank (26) before being recycled by the pump (2).

The implementations described previously may also be modified in such a way as to make the method of the invention entirely continuous.

Consequently, another object of the invention relates to a film coating method such as described above in which continuous spraying is performed in a film coating drum whose axis is inclined with relation to the horizontal, for example inclined 5°, allowing continuous circulation of the tablets introduced in the upper part of the drum and collected after film coating in the lower part of this drum.

According to a first implementation by continuous path, one may utilize an installation such as represented in Fig. 1 but modified according to Fig. 3, that is, an installation in which the film coating drum (13) is slightly inclined with relation to the horizontal in order to allow not only the rotation of tablets but also their slow longitudinal displacement in the drum. The length and obliquity of the rotary assembly (13) are, furthermore, calculated in such a way as to maintain a retention time suitable for complete and rapid film coating.

On the other hand, a hopper (27) and a container (28) are connected, one to the input situated upstream and to the upper part of the drum (13) in order to allow the introduction of tablets in a semi-continuous manner, the other downstream and at its lower part in such a way as to collect the film coated tablets.

Furthermore, a ramp (29) of several nozzles (12) disposed in parallel allows continuous spraying to be carried out on the tablets in movement in the rotating drum.

In such a system, it will be possible to modify the complete film coating time by modifying the size of the nozzle (12) openings as well as the obliquity of the drum according to the targeted result. Furthermore, the gas stream leaving the film-coating drum is treated by one or the other of the collection/recycling methods which are part of the implementations by discontinuous path described previously.

According to a variation of the method by continuous path above, spraying is carried out continuously in a film coating drum whose axis is inclined with relation to the horizontal, for example inclined 5°, allowing a continuous circulation of the tablets maintained under pressure in the drum, for example at a pressure between 30 and 200 bar and at a suitable temperature, for example at a temperature between 30 and 60°C, these tablets being introduced in the film coating drum thanks to a system of air locks situated upstream and at the upper part of said drum and collected, after film coating, downstream thanks to a system of air locks situated at the lower part of this drum, these air lock systems operating semi-continuously in such a way as to maintain a pressure in the drum in question, for example a pressure between 30 and 200 bar.

Therefore, according to a second implementation by continuous path, an installation such as represented in Fig. 2 but modified according to Fig. 4 may be used, that is, an installation wherein the film coating drum (13) is placed in a container (18) that may withstand a pressure of 200 bar.

Its axis, as that of the container under pressure (18) that contains it, is slightly inclined with relation to the horizontal in order to allow not only the rotation of the tablets but also their slow longitudinal displacement in the drum. Furthermore, the length and obliquity of the rotary assembly are calculated in order to maintain a retention time that is suitable for complete and rapid film coating.

Moreover, two air locks (30) and (31) are connected, one to the input situated at the upper part of the drum (13), the other to its lower part. They may be pressurized by a solvent fluid flow derived from that which ensures sweeping of the drum (13). In addition, a ramp (29) of several nozzles (12), disposed in parallel and according to the axis of the drum (13), produces continuous spraying on the tablets in movement in the rotating drum.

In such a system, it is possible to modify the total film coating time by modifying the size of the nozzle openings as well as the obliquity of the drum, according to the targeted result. Moreover, this system allows the continuous introduction of tablets via the air lock (30) and their collection according to a comparable quantity via the air lock (31) and the container (28) in view of, for example, bagging the tablets on line. Lastly, as in the previous discontinuous implementations, the gas stream leaving the film-coating drum may be treated by the collection/recycling methods described.

The following non-limiting examples illustrate the method of the invention.

EXAMPLE 1

Film coating of pharmaceutical tablets containing valproic acid and its sodium salt (discontinuous path)

In an installation such as illustrated in Fig. 1, film coating is carried out on a lot of scored tablets from an average unit weight of 730 mg containing a pharmaceutical active ingredient comprised of valproic acid and its sodium salt as well as an excipient comprised of cellulosic derivatives, silica and sodium saccharin with a film coating agent comprised of a mixture containing equal parts a polyacrylate, a polyethylene glycol, a methylhydroxypropyl-cellulose type cellulose derivative, talc and titanium dioxide, this film coating leading to a delayed assimilation of the medication.

Under agitation for 12 hours, first the film-coating agent is suspended in absolute ethanol at a rate of 250 g of this agent for 750 g of ethanol. Then two liters of this suspension is introduced in the reactor (6) and put in contact with pure carbon dioxide maintained at 150 bar at 45°C. This mixture is maintained under agitation by means of an anchor type agitator rotating at the speed of 600 rotations per minute.

After 20 minutes of agitation, the suspension thus obtained is sent to the film coating drum (13) comprised of a horizontal axis cylinder with a diameter of 0.48m and a length of 0.32m, in which 5 kg of tablets is introduced. This suspension is suddenly released to atmospheric pressure through a nozzle (12) whose opening has a diameter of 350 µm. The film coating drum is rotated at a speed of 4 rotations per minute and is swept by a flow of 100 m^3/h of air heated to 50°C.

After 5 minutes, after having sprayed approximately 550 g of suspension, spraying is stopped and rotation of the drum and the supply of hot air are maintained for 5 minutes in order to eliminate the last traces of ethanol and carbon dioxide.

After this operation, the sweeping of hot air is stopped and the rotation of the drum is stopped to allow the tablets to be collected, the tablets are then observed in a binocular loupe and precisely weighed. The average weight of a film coated tablet therefore reaches 748 mg and nearly all of these tablets present an excellent surface appearance, similar to that obtained during the implementation of film coating by the method conventionally used from an aqueous suspension of a film coating agent. This film coating operation according to the prior method necessitates a process time on the order of 110 minutes with the same film coating drum as that used above, or 10 times more time than that used by the method, which is the subject of the present invention.

EXAMPLE 2

Film coating of pharmaceutical tablets containing valproic acid and its sodium salt (discontinuous path)

In an installation such as that illustrated in Fig. 2, the film coating of a lot of tablets identical to those used in Example 1 is carried out with an identical film-coating agent.

However, the film coating drum (13), if it is similar to that used in the installation of Fig. 1, is installed in a cylindrical enclosure (18) designed to withstand pressure that may reach 200 bar, the drum being rotated by a magnetic drive system ensuring good sealing at high pressure.

First, in a manner similar to that used in Example 1, the initial film coating agent suspension in ethanol is prepared and then the suspension in the reactor (6) is prepared in the presence of carbon dioxide at supercritical pressure with, however, the pressure within this reactor maintained at 190 bar.

After loading 5 kg of tablets, the assembly is closed and filled with carbon dioxide at 60 bar and 50°C. A stream of carbon dioxide is maintained under these pressure and temperature conditions due to a flow of 100 kg/h, the fluid leaving the drum then being released at approximately 45 bar in the relief valve (19), sent to the separators (20) and (21) and then recycled as described previously.

When equilibrium of the conditions is truly reached, spraying of the suspension produced in the reactor (6) is begun in the spraying drum (13) for 5 minutes via a nozzle that is identical to that used in Example 1. Also, as with the previous example, sweeping by carbon dioxide and rotation of the drum (13) is maintained for five minutes after stopping the spraying, then the fluid contained is emptied and the container (18) and the drum (13) are opened in order to collect the tablets. The weighing and observation of these tablets provide results that are very close to those obtained during Example 1 or to those obtained by implementing a conventional method, with an average unit weight of 751 mg. However, unlike Example 1, the emission of ethanol to the atmosphere was divided at least by 10, the largest part of the ethanol being collected in the separators (20-21) and drawn off from the air locks (22-23) at atmospheric pressure. A small proportion of this alcohol is carried along by the carbon dioxide and is therefore immediately recycled in this method. The emission of solvent into the atmosphere is limited to that emitted during the emptying of the film coating drum at the end of the operation, and carbon dioxide emissions are also divided by at least 10 with relation to those observed during Example 1.

EXAMPLE 3

Film coating of pharmaceutical tablets containing valproic acid and its sodium salt (continuous path)

In an installation such as [that] illustrated in Fig. 1 and 3, the film coating of a lot of 365 kg of tablets identical to those used in Example 1 is carried out with an identical film coating agent.

For this purpose, the initial suspension of this agent in ethanol is prepared, as described in Example 1, then the suspension in the reactor (6) is prepared in the presence of carbon dioxide at supercritical pressure. Furthermore, equipment that is similar to that used in Example 1 is used for the implementation of this film coating operation.

However, the film-coating drum (13) with a diameter of 0.48 m and a length of 1.50 m is inclined 5° with relation to the horizontal. Furthermore, the equipment provides the possibility of semi-continuously introducing 2 to 3 kg of tablets into a hopper (27) connected to the drum (13) by vertical piping with a diameter of 0.05 m connected to the highest part of the drum (13) and collecting in the container (28), approximately every 2 minutes, a similar quantity by vertical piping with the same diameter as the previous, connected to the lowest part of the drum (13).

The film coating method may be implemented in a nearly continuous manner, the reactor (6) being supplied, first, by a 10 kg/h flow of film coating agent suspension by the pump (5) adjusted by a level sensor disposed within the reactor (6) and on the other hand by carbon dioxide at supercritical pressure by the pump (2) at the flow required to maintain a pressure of 150 bar in the reactor in question.

The spraying is continuously carried out across a ramp (29) of four parallel nozzles (12), similar to those used in the previous examples, these nozzles being disposed according to the axis of the drum (13).

The film coating operation is implemented in a manner similar to that described in Example 1: the film coating drum is rotated at a speed of 4 rotations/minute and is swept by a flow of 100 m^3/h of air (16) heated to 50°C. During a period of 6 hours, the lot of 365 kg of tablets may therefore be film coated in a very satisfactory manner, the average weight of the tablets after treatment being 752 mg.

EXAMPLE 4

Film coating of pharmaceutical tablets containing valproic acid and its sodium salt (continuous path)

In an installation such as illustrated in Fig. 1 and 4, the film coating of a 345 kg lot of tablets identical to those used in Example 1 is carried out with an identical film coating agent.

For this purpose, the initial suspension of this agent in ethanol, then the suspension in the reactor (6) in the presence of carbon dioxide at supercritical pressure, are prepared as described in Example 1.

Furthermore, equipment similar to that used in Example 2 is utilized for the implementation of this operation. However, the film coating drum (13) with a diameter of 0.48 m and a length of 1.50 m, placed in a container (18) that contains the drum, is inclined 5° with relation to the horizontal. Furthermore, two 10-liter air locks (30) and (31) are connected to the input and the output of the drum (13). These air locks may be pressurized by a stream of carbon dioxide derived from that which ensures sweeping of the drum (13) and allows 2 to 3 kg of tablets to be semi-continuously introduced and allows a similar quantity to be extracted, approximately every two minutes.

The film coating method may be implemented in a nearly continuous manner, the reactor (6) being supplied first by a flow of the film coating agent suspension at 10 kg/h by the pump (5) adjusted by a level sensor placed within the reactor (6) and on the other hand by supercritical carbon dioxide by the pump (2) at the flow required to maintain a pressure of 190 bar in the reactor in question.

Spraying is continuously carried out across a ramp (29) of 4 parallel nozzles (12), similar to those used in the previous examples, these nozzles being disposed according to the axis of the film coating drum.

Decompression of the fluid stream from the drum (13), separation and collection of the ethanol via separators (20) and (21) and air locks (22) and (23) as well as recycling of the carbon dioxide are carried out in a manner similar to that described in Example 2.

During a period of 6 hours, the 345 kg lot of tablets may therefore be film coated in a very satisfactory manner, with a total ethanol emission of 5.8 kg and a carbon dioxide consumption of 183 kg.

EXAMPLE 5

Tablet film coating containing clopidogrel

By using the same method as that described in Example 2, a 6 kg lot of tablets with an average unit weight of 240 mg comprising clopidogrel as the active ingredient is film coated with a film coating agent comprised of a mixture containing a phthalate polyvinyl acetate copolymer, from a suspension of 400 g of this film coating agent in 1600 g of ethanol. This suspension is put in contact with pure carbon dioxide maintained at the supercritical state under temperature and pressure conditions of 50°C and 150 bar and the film coating operation is proceeded with for 20 minutes.

At the end of this operation, tablets with an average weight of 243.6 mg are obtained. Nearly all of these tablets present a satisfactory film coating.

CLAIMS

1. A method for film coating tablets, characterized in that a suspension of a film coating agent in a fluid at supercritical pressure is sprayed on said tablets.
2. The method according to Claim 1, characterized in that continuous spraying is carried out in a film coating drum whose axis is inclined with relation to the horizontal allowing continuous circulation of the tablets introduced upstream and at the upper part of this drum and, after film coating, collection downstream and at the lower part of said drum.
3. The method according to Claim 1 or 2, characterized in that the continuous spraying is carried out in a film coating drum whose axis is inclined with relation to the horizontal allowing continuous circulation of the tablets maintained at a suitable temperature and under pressure in said drum, these tablets being introduced in the drum thanks to a system of air locks situated upstream and at the upper part of this drum and, after film coating, collected downstream thanks to a system of air locks situated at the lower part of said drum, these air lock systems operating by semi-continuous path in such a way as to maintain pressure in said drum.
4. The method according to one of Claims 1 to 3, characterized in that spraying is carried out on tablets maintained in continuous agitation.
5. The method according to one of Claims 1 to 4, characterized in that the suspension of the film coating agent in the fluid at supercritical pressure is formed from:

   - either a film coating agent introduced as is in the fluid at supercritical pressure, possibly containing one or more co-solvents chosen from among C_1-C_4 alcohols and C_3-C_6 esters.

   - or a suspension of a film coating agent in one or more solvents chosen from among C_1-C_4 alcohols, and C_3-C_6 esters introduced in the fluid at supercritical pressure, possibly containing one or more co-solvents chosen from among C_1-C_4 alcohols and C_3-C_6 esters.
6. The method according to Claim 5, characterized in that the film coating agent suspension in the solvent(s) varies from 5% to 30% of the weight of the total suspension.

7. The method according to Claim 5 or 6, characterized in that the solvent or co-solvent is ethanol.
8. The method according to one of Claims 1 to 7, characterized in that the quantity of the film coating agent in the fluid at supercritical pressure does not exceed 30% of the weight of the latter.
9. The method according to one of Claims 3 to 8, characterized in that the pressure is between 30 and 200 bar.
10. The method according to one of Claims 3 to 9, characterized in that the temperature is between 30 and 60°C.
11. The method according to one of Claims 1 to 9, characterized in that the film coating agent is chosen from among cellulose derivatives, hydroxylated cellulose derivatives, microcrystalline cellulose, a polyacrylate, a polyvinyl alcohol, a polyethylene, a polypropylene, a polyethylene glycol, a polystyrene, a polyacrylamide, an ethylvinylacetate polyvinyl acetate copolymer, a polyvinyl acetate phthalate copolymer, a polyvinylpyrrolidone, titanium oxide, wax.
12. The method according to one of Claims 1 to 11, characterized in that the fluid at supercritical pressure is carbon dioxide at supercritical pressure.

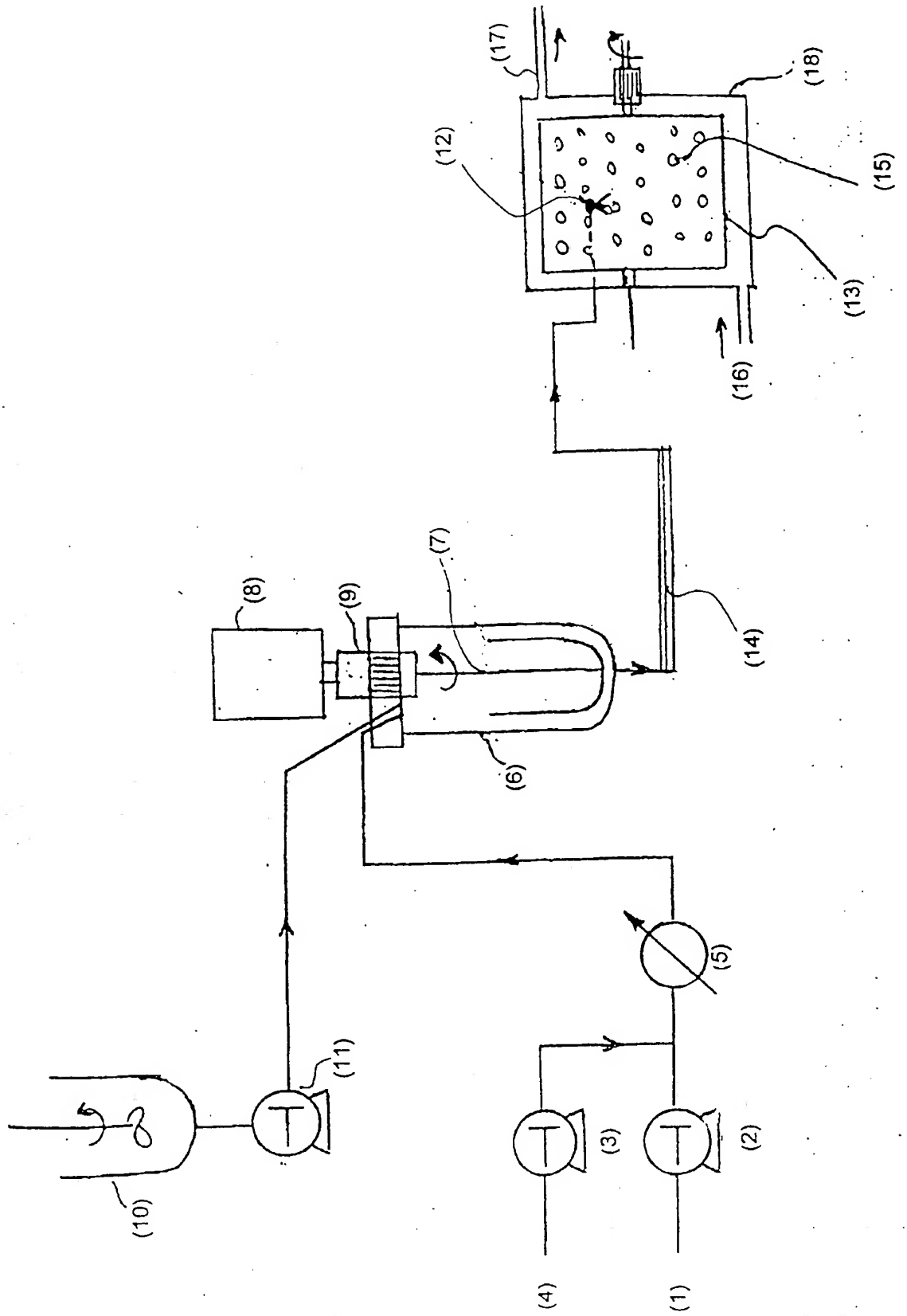

FIG. 1

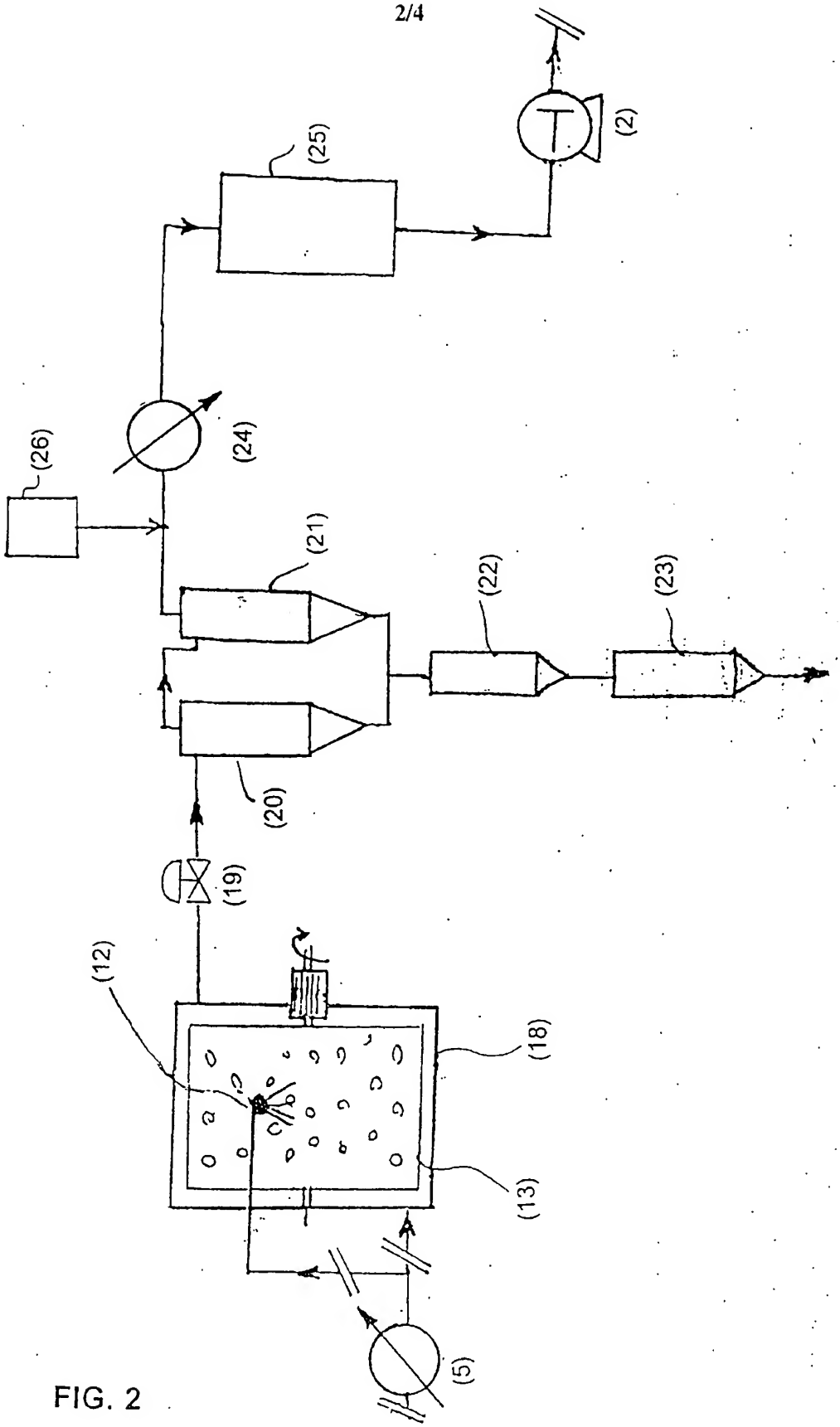

FIG. 2

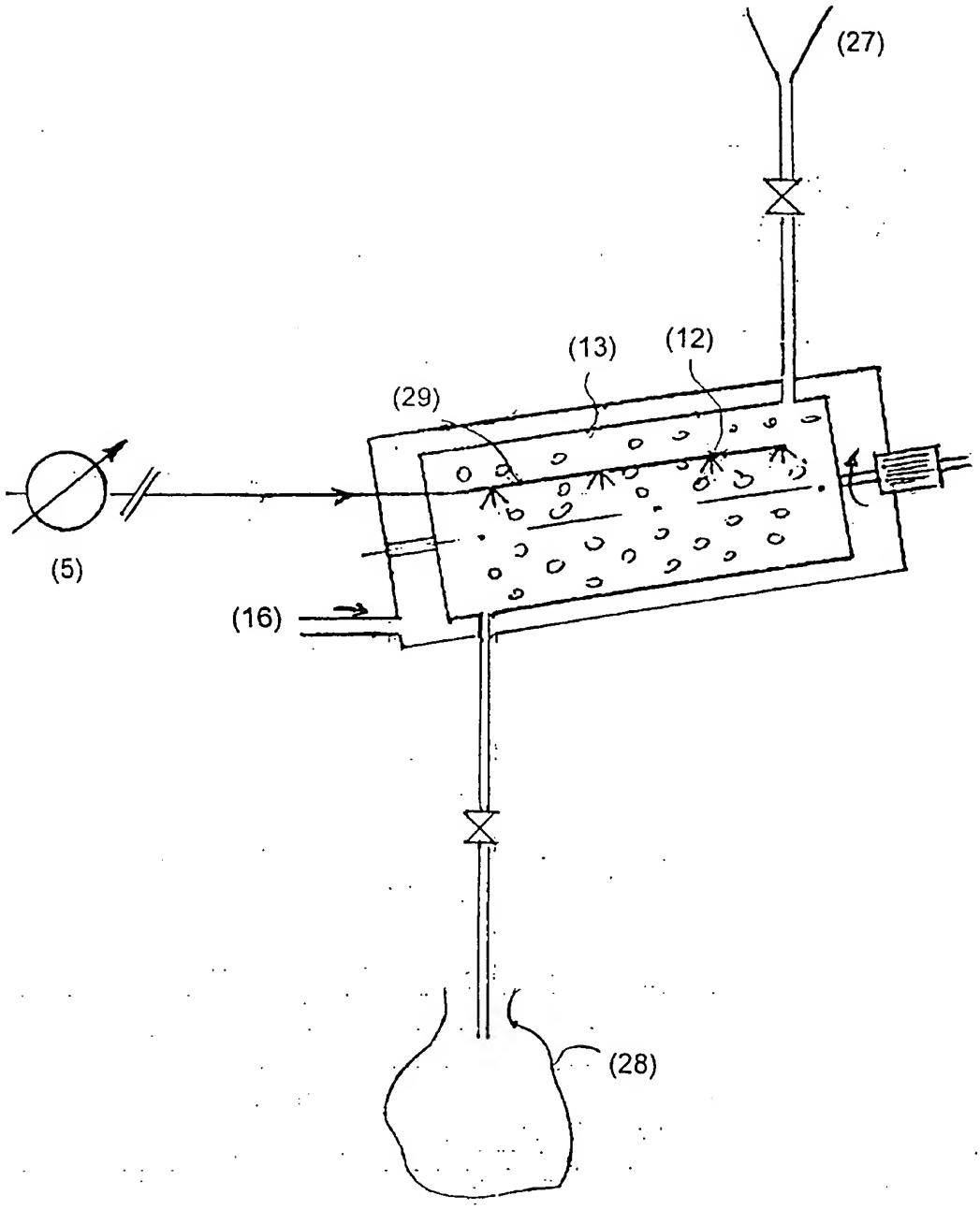

FIG. 3

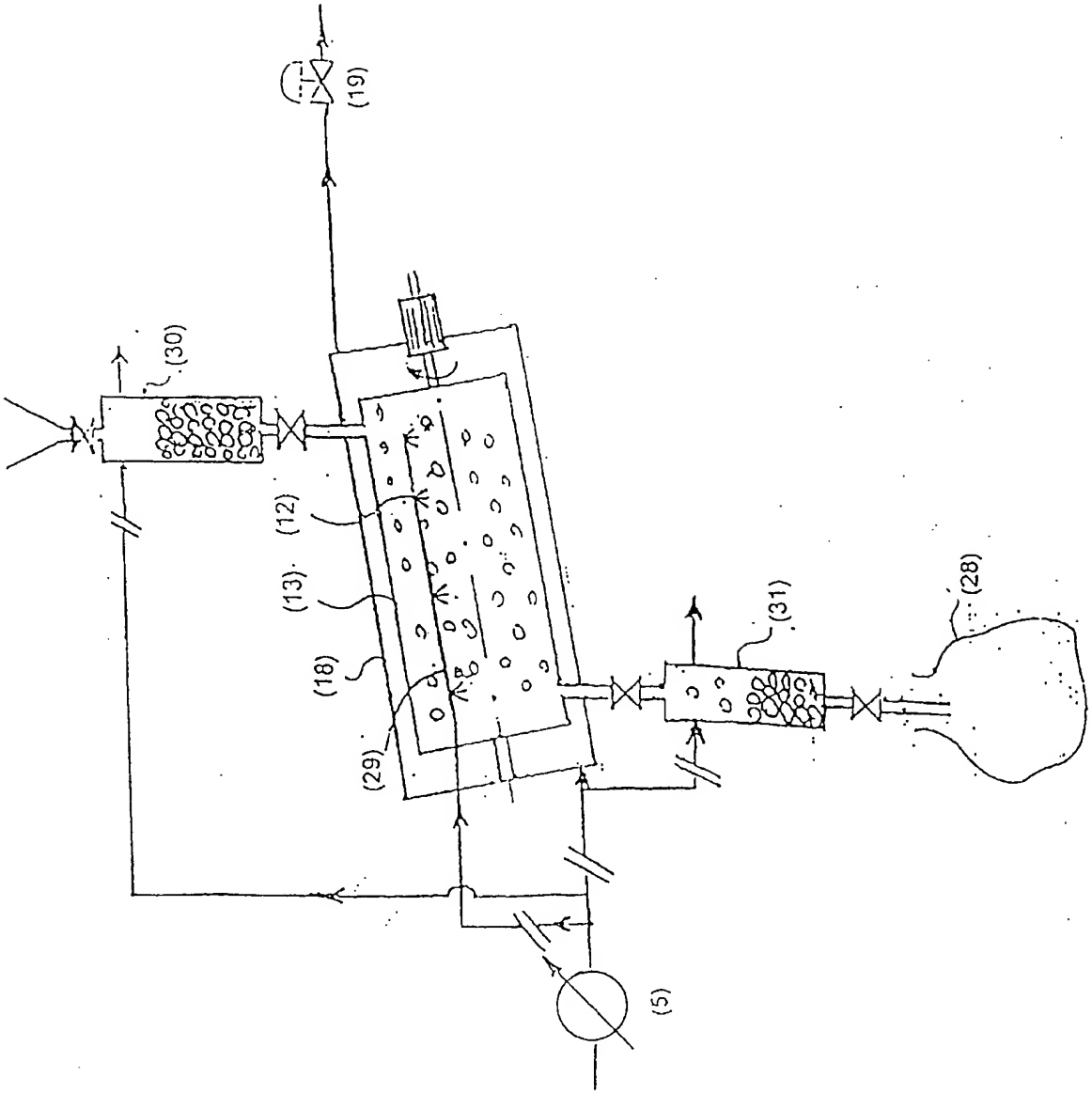

FIG. 4

INTERNATIONAL SEARCH REPORT

Inte ›nal Application No
PCT/FR 00/03127

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K9/28

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, BIOSIS, CHEM ABS Data, MEDLINE, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5 178 325 A (NIELSEN KENNETH A) 12 January 1993 (1993-01-12) column 3, line 35 - line 38 column 12, line 24 - line 28 column 15, line 55 -column 16, line 4 column 16, line 23 - line 25 column 16, line 55 -column 17, line 2 column 18, line 20 - line 31; claim 1 ---	1-12
A	EP 0 492 535 A (UNION CARBIDE CHEM PLASTIC) 1 July 1992 (1992-07-01) page 4, line 14 - line 34 page 6, line 40 - line 47 page 17, line 30 - line 33 claims 1,2; examples --- -/--	1-12

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
22 February 2001	07/03/2001

Name and mailing address of the ISA	Authorized officer
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INTERNATIONAL SEARCH REPORT

Inte onal Application No
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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A	PHILLIPS E M ET AL: "RAPID EXPANSION FROM SUPERCRITICAL SOLUTIONS: APPLICATION TO PHARMACEUTICAL PROCESSES" INTERNATIONAL JOURNAL OF PHARMACEUTICS,NL,AMSTERDAM, vol. 94, 1993, pages 1-10, XP000675504 ISSN: 0378-5173 page 1, column 1, line 8 - line 1 page 3, column 2, line 3 - line 18 page 7, column 2, last paragraph -page 8, column 1, paragraph 1 ---	1-12
A	EP 0 706 821 A (MICROENCAPSULATION CENTRE) 17 April 1996 (1996-04-17) page 2, column 1, line 58 -column 2, line 4 page 2, column 2, line 57 -page 3, column 3, line 8 page 5, column 7, line 39 - last line page 7, column 11, line 10 - line 48; claim 11; examples -----	1-12

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INTERNATIONAL SEARCH REPORT

Inter nal Application No
PCT/FR 00/03127

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US 5178325 A	12-01-1993	NONE	
EP 0492535 A	01-07-1992	AU 638620 B	01-07-1993
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		KR 9711709 B	14-07-1997
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		WO 9211310 A	09-07-1992
EP 0706821 A	17-04-1996	AT 176764 T	15-03-1999
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		WO 9611055 A	18-04-1996
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		GR 3030282 T	30-09-1999
		JP 10510243 T	06-10-1998
		US 6087003 A	11-07-2000

RAPPORT DE RECHERCHE INTERNATIONALE

Der e Internationale No
PCT/FR 00/03127

A. CLASSEMENT DE L'OBJET DE LA DEMANDE
CIB 7 A61K9/28

Selon la classification internationale des brevets (CIB) ou à la fois selon la classification nationale et la CIB

B. DOMAINES SUR LESQUELS LA RECHERCHE A PORTE

Documentation minimale consultée (système de classification suivi des symboles de classement)
CIB 7 A61K

Documentation consultée autre que la documentation minimale dans la mesure où ces documents relèvent des domaines sur lesquels a porte la recherche

Base de données électronique consultee au cours de la recherche internationale (nom de la base de donnees, et si réalisable, termes de recherche utilisés)
EPO-Internal, WPI Data, PAJ, BIOSIS, CHEM ABS Data, MEDLINE, EMBASE

C. DOCUMENTS CONSIDERES COMME PERTINENTS

Catégorie °	Identification des documents cités, avec, le cas echéant, l'indication des passages pertinents	no. des revendications visees
A	US 5 178 325 A (NIELSEN KENNETH A) 12 janvier 1993 (1993-01-12) colonne 3, ligne 35 - ligne 38 colonne 12, ligne 24 - ligne 28 colonne 15, ligne 55 -colonne 16, ligne 4 colonne 16, ligne 23 - ligne 25 colonne 16, ligne 55 -colonne 17, ligne 2 colonne 18, ligne 20 - ligne 31; revendication 1 ---	1-12
A	EP 0 492 535 A (UNION CARBIDE CHEM PLASTIC) 1 juillet 1992 (1992-07-01) page 4, ligne 14 - ligne 34 page 6, ligne 40 - ligne 47 page 17, ligne 30 - ligne 33 revendications 1,2; exemples --- -/--	1-12

[X] Voir la suite du cadre C pour la fin de la liste des documents

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22 février 2001	07/03/2001

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Den e Internationale No
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C.(suite) DOCUMENTS CONSIDERES COMME PERTINENTS

Catégorie °	Identification des documents cités, avec,le cas échéant, l'indicationdes passages pertinents	no. des revendications visées
A	PHILLIPS E M ET AL: "RAPID EXPANSION FROM SUPERCRITICAL SOLUTIONS: APPLICATION TO PHARMACEUTICAL PROCESSES" INTERNATIONAL JOURNAL OF PHARMACEUTICS,NL,AMSTERDAM, vol. 94, 1993, pages 1-10, XP000675504 ISSN: 0378-5173 page 1, colonne 1, ligne 8 - ligne 1 page 3, colonne 2, ligne 3 - ligne 18 page 7, colonne 2, dernier alinéa -page 8, colonne 1, alinéa 1 ---	1-12
A	EP 0 706 821 A (MICROENCAPSULATION CENTRE) 17 avril 1996 (1996-04-17) page 2, colonne 1, ligne 58 -colonne 2, ligne 4 page 2, colonne 2, ligne 57 -page 3, colonne 3, ligne 8 page 5, colonne 7, ligne 39 - dernière ligne page 7, colonne 11, ligne 10 - ligne 48; revendication 11; exemples -----	1-12

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Formulaire PCT/ISA/210 (suite de la deuxième feuille) (juillet 1992)

RAPPORT DE RECHERCHE INTERNATIONALE

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PCT/FR 00/03127

Document brevet cité au rapport de recherche	Date de publication	Membre(s) de la famille de brevet(s)	Date de publication
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